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Dated 15 July 2004

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15JUL03 E822470-2 010185
P01/7700 0.00-0316439.9

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Request for grant of a patent

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The Patent Office

Cardiff Road
Newport
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1	Your reference	SYN 60018
2	Patent application number *(The Patent Office will fill in this part)*	15 JUL 2003 **0316439.9**
3	Full name, address and postcode of the or of each applicant (underline all surnames)	JOHNSON MATTHEY PLC 2-4 Cockspur Street, Trafalgar Square, London, SW1Y 5BQ
	Patents ADP Number *(if you know it)*	08519803001
	If the applicant is a corporate body, give the country/state of its incorporation	United Kingdom
4	Title of the invention	Catalysts
5	Name of Your Agent *(if you have one)*	GIBSON, Sara Hillary Margaret
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	Johnson Matthey Catalysts Intellectual Property Department PO Box 1, Belasis Avenue Billingham Cleveland England, TS23 1LB
	Patents ADP Number *(if you know it)*	08652166001
6	If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number	Country / Priority Application number *(if you know it)* / Date of Filing *(day / month / year)*
7	If this application is divided or otherwise derived from an earlier UK application, give the number and filing date of the earlier application	Number of earlier application / Date of Filing *(day / month / year)*
8	Is a statement of inventorship and of right to grant of a patent required in support of this request?	Yes

Answer yes if:
a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
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Continuation sheets of this form	-
Description	18
Claim(s)	3
Abstract	1
Drawings	-

10 If you are also filing any of the following state how many against each item

Priority documents	
Translations of priority documents	
Statement of Invention and right to grant of a patent *(Patents Form 7/77)*	
Request for Preliminary Examination and search *(Patents Form 9/77)*	
Request for Substantive Examination *(Patents Form 10/77)*	
Any other documents *(Please specify)*	

11 I/We request the grant of a patent on the basis of this application

Signature S.H.M. Gibson

Date 14.7.2003

12 Name and daytime telephone number of person to contact in the United Kingdom

Sara H.M. Gibson
01642 522650

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Catalysts

This invention relates to transition metal catalysts for performing asymmetric hydrogenation reactions and in particular to transition metal catalysts for the asymmetric hydrogenation of ketones and imines.

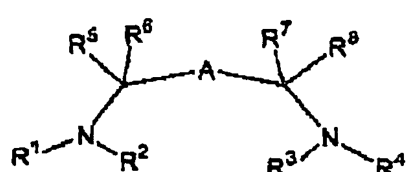
Transition metal catalysts particularly those based on chiral ruthenium (Ru) phosphine complexes are known to be effective for the asymmetric hydrogenation of ketones. EP-B-0718265 describes the use of chiral Ru-bis(phosphine)-1,2-diamine complexes for the hydrogenation of ketones to produce chiral alcohols. Similarly, WO 01/74829 describes a chiral Ru-Phanephos-1,2-diamine complex for the asymmetric hydrogenation of ketones.

Although it is accepted that the combination of bis(phosphine) and the chiral diamine ligands are important for achieving a high enantiomeric excess (ee) and a wide range of phosphine ligands has been described, only 1,2-diamine ligands have been considered heretofore. By the term "1,2-diamines" we mean diamines wherein the carbon atoms to which the amine functionalities are bound are directly linked. Such diamines include chiral substituted ethylenediamine compounds such as (S,S)-diphenylethylenediamine ((S,S)-Dpen). Without wishing to be bound by any theory we believe that this is due to the perceived need for the resulting conformationally-stable 6-membered ring structure that forms when 1,2-diamines co-ordinate to the metal atom. Larger ring structures, for example those formed using 1,3- or 1,4-diamines can be less conformationally-stable and therefore may be expected to provide catalysts that give lower enantiomeric excesses than the corresponding catalysts prepared using 1,2-diamines.

Accordingly the chiral catalysts heretofore comprise 1,2-diamines and have relied principally upon variation of the structure of the phosphine ligand to improve their enantioselectivity. Although effective for some substrates such as acetophenone, a range of ketone and imine substrates remain unreactive to the existing catalysts or are obtained with undesirably low enantiomeric excesses.

We have found surprisingly that chiral catalysts suitable for the hydrogenation of ketones and imines may comprise diamines that provide larger ring structures and that such catalysts can provide higher enantiomeric excesses than those comprising 1,2-diamines.

Accordingly the invention provides a chiral catalyst comprising the reaction product of a group 8 transition metal compound a chiral phosphine and a chiral diamine of formula (I)



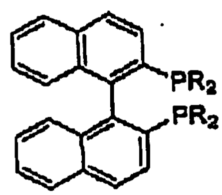
(I)

in which R^1, R^2, R^3 or R^4 are independently hydrogen, a saturated or unsaturated alkyl, or cycloalkyl group, an aryl group, a urethane or sulphonyl group and R^5, R^6, R^7 or R^8 are independently hydrogen, a saturated or unsaturated alkyl or cycloalkyl group, or an aryl group, at least one of R^1, R^2, R^3 or R^4 is hydrogen and A is a linking group comprising one or two substituted or unsubstituted carbon atoms.

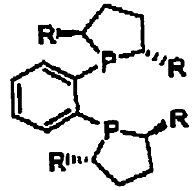
The group 8 transition metal compound may be a compound of cobalt (Co), nickel (Ni), ruthenium, (Ru), rhodium (Rh), iridium (I), palladium (Pd) or platinum (Pt). For hydrogenation of ketones and imines the transition metal compound is preferably a compound of ruthenium.

The metal compound may be any metal compound that is able to react with the phosphine and the chiral diamine (I) to provide a metal complex catalyst. The metal compound is preferably a metal salt, e.g. halide, carboxylate, sulphonate or phosphonate, or an organometallic compound. Particularly suitable metal compounds include $[RuCl_2(benzene)]_2$ and $[RuCl_2(cymene)]_2$.

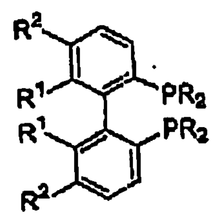
The chiral phosphine may be a monodentate or bidentate phosphine. Preferably the chiral phosphine is a chiral bis(phosphine). A range of chiral bis(phosphines) are known and may be used in the present invention. Suitable chiral bis(phosphines) include but are not restricted to the following structural types;



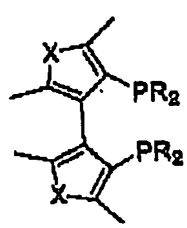
BINAP, R = aryl and alkyl



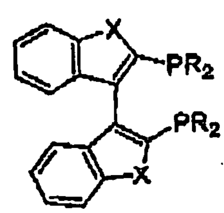
DUPHOS
R= alkyl, alkoxy, hydroxy, amino, aryl



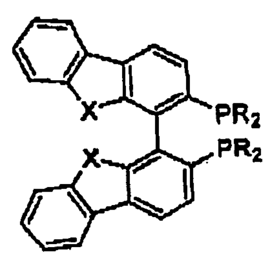
BIPHEP
R= aryl and alkyl
R^1= alkyl, alkoxy
R^2= H, alkyl, alkoxy



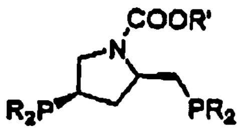
TMBTP
R= aryl, alkyl
X = O, S, N



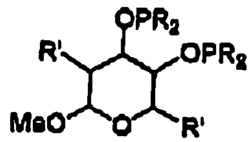
BITIANAP
R= aryl, alkyl
X = O, S, N



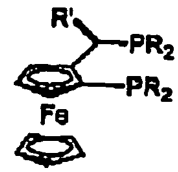
BIBFUP
R = aryl, alkyl
X = O, S, N



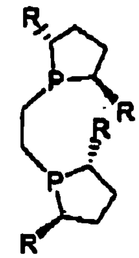
bppm
R = Aryl, Alkyl
R' = Alkyl



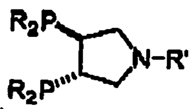
CARBOPHOS
R = aryl
R' = $CH_2C(O)Ph$



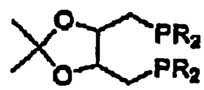
JOSIPHOS
R = alkyl, aryl
R' = alkyl, aryl



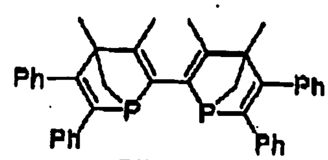
BPE
R = alkyl



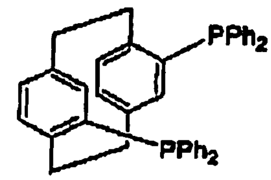
DEGPHOS
R = aryl
R' = H, Benzyl



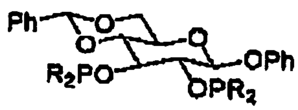
DIOP
R = aryl



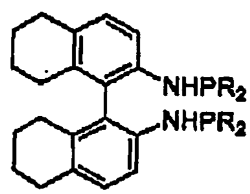
BIPNOR



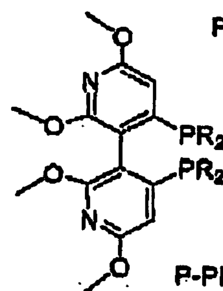
PHANEPHOS



SELKE
R = Ph



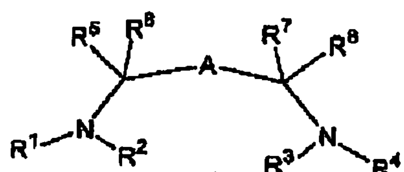
BINAPAN
R = aryl, alkyl



P-PHOS
R = aryl

Preferably, the chiral phosphine is based on BINAP, DUPHOS, PHANEPHOS, and P-PHOS.

The chiral diamine is of formula (I)



(I)

In which R^1, R^2, R^3 or R^4 are independently hydrogen, a saturated or unsaturated alkyl, or cycloalkyl group, an aryl group, a urethane or sulphonyl group and R^5, R^6, R^7 or R^8 are independently hydrogen, a saturated or unsaturated alkyl or cycloalkyl group, or an aryl group, at least one of R^1, R^2, R^3 or R^4 is hydrogen and A is a linking group comprising one or two substituted or unsubstituted carbon atoms.

Herein the term "alkyl" is meant to encompass straight chain or branched alkyl groups (e.g. C1-C20) such as methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, sec-butyl, tert-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, dodecyl, and stearyl, "cycloalkyl" is meant to encompass (e.g. C3-C10) cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or adamantyl, and "aryl" is meant to encompass aromatic groups such as phenyl (Ph), naphthyl (Np) or anthracyl and heteroaryl groups such as pyridyl. The alkyl groups may be optionally substituted with one or more substituents such as halide (Cl, Br, F or I) or alkoxy groups, e.g. methoxy, ethoxy or propoxy groups. The aryl groups may be optionally substituted with one or more substituent such as halide (Cl, Br, F or I), alkyl (C1-C20) alkoxy (C1-C20), amino (NR_2, where R = hydrogen or alkyl), hydroxy, halide (e.g. Cl, Br or F), carboxy (CO_2R', R' = H or alkyl) or sulphonate groups. Suitable substituted aryl groups include 4-methylphenyl (tolyl), 3,5-dimethylphenyl (xylyl), 4-methoxyphenyl and 4-methoxy-3,5-dimethylphenyl.

R^1, R^2, R^3 and R^4 may be the same or different and are preferably selected from hydrogen or methyl, ethyl, isopropyl, cyclohexyl, phenyl or 4-methylphenyl groups.

In one embodiment, R^1 and R^2 are linked or R^3 and R^4 are linked so as to form a 4 to 7-membered ring structure, preferably a 5- or 6-membered ring structure, incorporating the nitrogen atom.

Most preferably R^1, R^2, R^3, R^4 are the same and are hydrogen.

R^5, R^6, R^7 and R^8 may be the same or different and are preferably hydrogen, methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, sec-butyl, tert-butyl, cycloalkyl groups such as cyclohexyl, aryl groups such as substituted or unsubstituted phenyl or naphthyl groups.

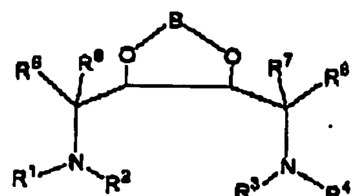
In one embodiment one or more of R^5, R^6 R^7 or R^8 may form one or more ring structures with the linking group A. The ring structure may comprise an alkyl or heteroalkyl 4- to 7-membered ring, preferably a 5- or 6-membered ring or may be an aromatic ring structure, e.g. aryl or hetero-aryl.

In EP-B-0718265 it was suggested that the nitrogen atoms of the diamine should be bound to chiral centres (centers of asymmetricity, p7, line line 2). We have found surprisingly that the chirality need not reside in these carbon atoms but may suitably be present in other parts of the diamine molecule, e.g. within R^5, R^6, R^7 or R^8 or linking group A.

The diamine ligand (I) is chiral. Preferably R^5, R^6, R^7 or R^8 or linking group A are chosen such that the ligand may be homochiral, i.e. (R,R) or (S,S) or have one (R) and one (S) centre. Preferably the chiral diamine is homochiral.

Linking group A provides a link between the carbon atoms to which the amine groups $-NR^1R^2$ and $-NR^3R^4$ are bound and comprises one or two substituted or unsubstituted carbon atoms. Substituting groups may replace one or both hydrogen atoms on the carbon atoms. The substituting groups may comprise one or more alkyl (C1-C20), alkoxy (C1-C20) or amino (NR_2, where R = hydrogen or alkyl) groups. The substituting groups may form one or more ring structures, e.g. a 4 to 7-membered ring structures incorporating one or more carbon atoms making up the linking group. Thus linking group A may comprise one or two carbon atoms forming part of one or more aromatic ring structures.

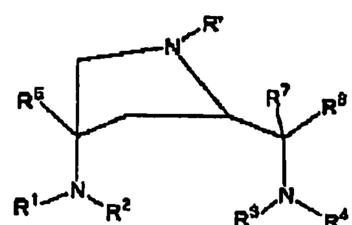
In one embodiment, the diamine is of formula (II)



(II)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are as previously described and B is a linking group comprising one or two substituted or unsubstituted carbon atoms. Preferably R^1, R^2, R^3, R^4 are hydrogen, R^5, R^6, R^7 and R^8 are hydrogen or alkyl groups and B comprises $C(CH_3)_2$ or $(CH_3)(OCH_3)C\text{-}C(CH_3(OCH_3)$.

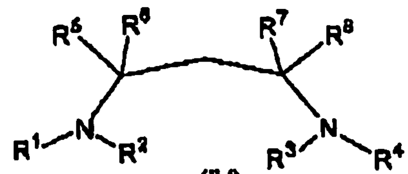
In a further embodiment, the diamine is of formula (III)



(III)

wherein R^1, R^2, R^3, R^4, R^5, R^7 and R^8 are as previously described and R' is a protecting group. Preferably R^1, R^2 and R^5 are hydrogen, R^3 and R^4 are hydrogen or alkyl, R^7 and R^8 are hydrogen, alkyl or aryl. It will be understood by persons skilled in the art that a wide range of protecting groups R' may be used for example alkyl, aryl, carboxylate, amido or sulphonate protecting groups may be used, e.g. benzyl ($CH_2C_6H_5$), methyl, tert-butyl, allyl, phenyl and substituted phenyls, $CO_2C(CH_3)_3$ (Boc), $CO_2CH_2C_6H_5$ (Cbz), ethyl carbonate, formamide, acetamides, benzamides, tosyl (Ts) and mesyl (Ms).

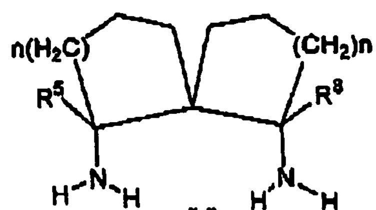
In a further embodiment, the diamine is of formula (IV)



(IV)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are as previously described. Preferably R^1, R^2, R^3, R^4, R^6, R^7 are hydrogen and R^5 and R^8 are aryl or substituted aryl, more preferably C_6H_5 or $C_{10}H_7$.

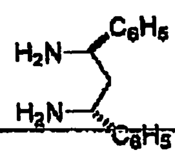
In a further embodiment, the diamine has R^1, R^2, R^3, R^4 are hydrogen and is of formula (V)



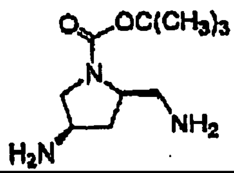
(V)

wherein R^5 and R^8 are as previously described and n = 1 or 2. Preferably R^5 and R^8 are hydrogen.

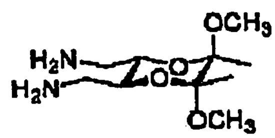
Thus suitable chiral diamines include but are not restricted to the following;



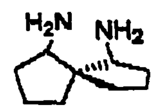
Dppn



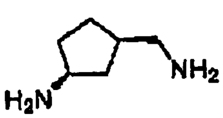
PyrBD

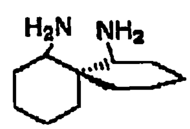


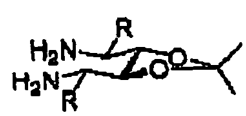
DioBD



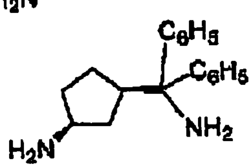
cis,cis - SpiroDiamine

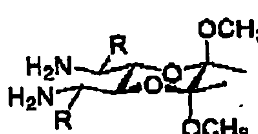






R = H, alkyl, aryl





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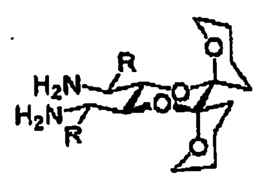
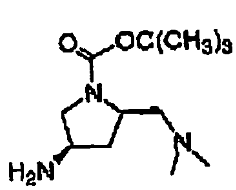
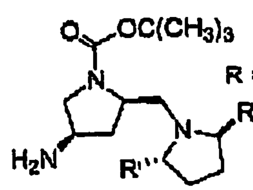
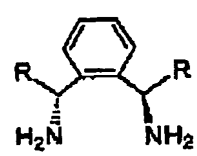


R = H, alkyl, aryl



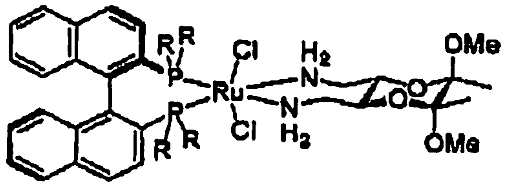
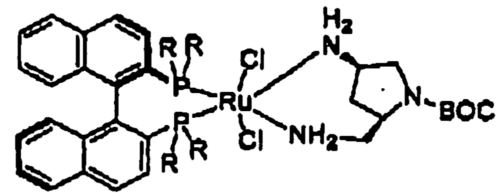
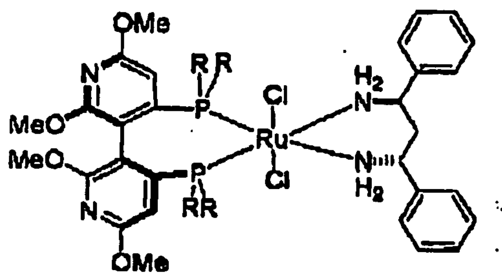
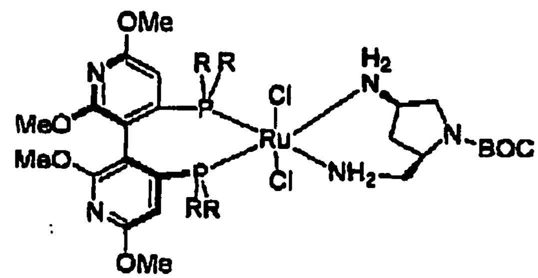


R = alkyl, aryl



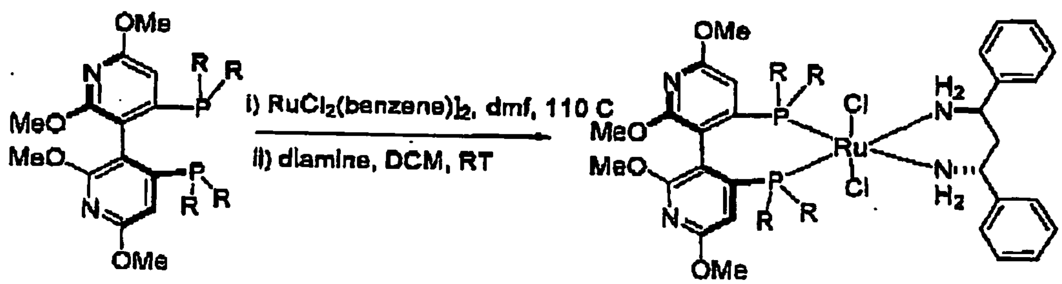
R = alkyl, aryl

Accordingly, group 8 transition metal catalysts of the present invention include but are not limited to the following;

where R = aryl, e.g. phenyl (Ph), tolyl (Tol) or xylyl (Xyl).

The catalysts of the present invention may be readily prepared from the metal compound, phosphine and diamine. In general, the metal compound is combined with the phosphine in a suitable solvent and heated if necessary and then the diamine is added to form the desired metal complex catalyst. For example, P-Phos reacts under relatively mild conditions with $[RuCl_2(benzene)_2]_2$ and then 1,3-Dppn to form a catalyst suitable for performing asymmetric hydrogenation reactions. This reaction is depicted below.



where R = aryl

The chiral metal complex catalysts of the present invention may be applied to a number of asymmetric reactions used to produce chiral products. Such reactions include but are not limited to the asymmetric hydrogenation of ketones and imines. To achieve high levels of enantiomeric purity in the reaction it is preferred that the metal complex comprises a substantially enantiomerically-pure phosphine and 1,3- or 1,4-diamine ligands.

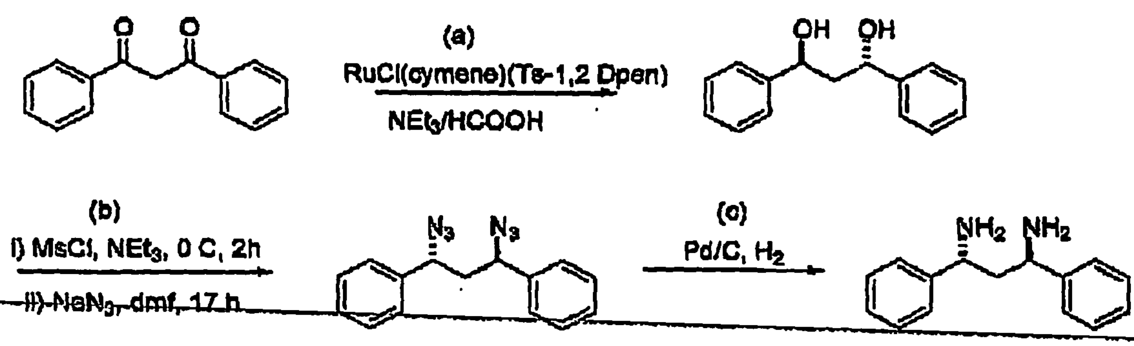
The conditions for using the metal complex catalysts are typically similar to those used for structurally related catalysts. For example, for the asymmetric reduction of ketones, the above catalyst may be used at room temperature under standard hydrogen pressures in combination with a strong base such as a sodium or potassium alkoxide, e.g. potassium tert-butoxide (KO^tBu) to yield chiral alcohols in high yield and enantiomeric excess.

Ketones and imines that may be reduced using catalysts of the present invention may be of formula RCXR' in which R and R' are substituted or unsubstituted, saturated or unsaturated alkyl, cycloalkyl or aryl groups which may be linked and form part of a ring structure, e.g. a 5 or 6 membered ring structure, and X is O (Oxygen) or NR" in which R" may be alkyl, cycloalkyl or aryl which may be linked to R and/or R' as part of a ring structure.

The invention is further illustrated by reference to the following examples. Unless otherwise stated room temperature was 20-25°C.

Example 1: Synthesis of Diphenyl-1,3-propanediamine (Dppn)

The diamine was prepared by the procedure of Roos et al. (Tetrahedron: Asymmetry 1999, 991-1000). The diol was prepared by transfer hydrogenation of the diketone by the procedure of Cossy (Tetrahedron Letters, 2001, 5005-5007).



(a) 1,3-Diphenyl-1,3-Propanediol

A mixture of dibenzyloylmethane (2.5 g, 0.0117 mol), [RuCl(cymene)(R,R)Ts-Diphenylethylenediamine] (78 mg, 0.117 mmol) in triethylamine/formic acid azeotropic mix (5:2, 0.0234 mol) and dichloromethane (10 ml) was heated at 40 °C for 48 hrs. The solvent was removed in vacuo and the residue poured into water (100 ml) which resulted in the precipitation of a colourless solid. The solid was dried and used in the next step without further purification.

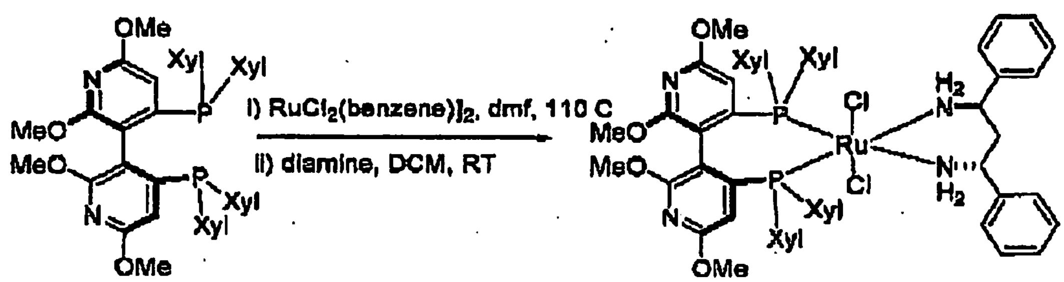
(b) 1,3-Diphenyl-1,3-Propanediazide

To the chiral 1,3-Diphenyl-1,3-Propanediol (0.150 g, 0.664 mmol) and triethylamine (0.205 g, 2.03 mmol) in tetrahydrofuran (THF) (5 ml) at 0°C under nitrogen was added methanesulfonyl

chloride (0.102 ml, 1.33 mmol). The mixture was allowed to warm to room temperature and stirred for 1 hr. The mixture was then filtered and the solid washed with a further portion of THF (5ml). The solvent was then removed in vacuo to leave the crude product. To this crude product was added dimethylformamide (DMF) (2 ml) and sodium azide (0.135 g, 2.08 mmol) and the mixture stirred at room temperature overnight. Thin layer chromatography (TLC) indicated complete conversion of the starting material. The DMF was removed in vacuo and methyl-tert-butyl ether (MTBE) added (25 ml). The organic layer was washed with water (25 ml) and brine (25 ml). The solvent was removed to yield the diazide as a colourless solid.
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.7 – 7.0 (10H, m, Ar-H), 4.7 (2H, t, CH), 2.0 (2H, t, CH_2).

(c) 1,3-Diphenyl-1,3-Propanediamine (dppn)
A mixture of the diazide (0.1g, 2.79 mmol) and Pd/C (10 wt % Pd, 0.010 g) was stirred in an autoclave under hydrogen gas (80psi) for 2 hrs. The hydrogen was released and the mixture filtered through celite. The solvent was removed to give the diamine as initially a colourless solid which was recrystallised by using a minimum amount of chloroform.
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.7 – 7.0 (10H, m, Ar-H), 3.9 (2H, t, CH), 2.0 (2H, t, CH_2).

Example 2: Preparation of Dppn-catalysts
a) Preparation of Ru[Cl_2((*R*/*S*)-Xyl-P-Phos)((*R*,*R*)-DPPN)].



A solution of (R)- or (S)-Xyl-P-Phos (100 mg, 0.132 mmol) and [$RuCl_2$(benzene)] dimer (31.5 mg, 0.063 mmol) in Dimethylformamide (1 ml) was heated at 100 C for 2.5 hrs under N_2. The dark red reaction mixture was cooled to room temperature. To this crude complex was added a solution of the (R,R)-Dppn diamine (0.138 mmol) in dichloromethane (1 ml) under nitrogen. The brown solution was stirred at room temperature overnight after which the solvent was removed in vacuo to yield the crude complex as a brown solid.

Trans-Ru[Cl_2((*R*)-Xyl-P-Phos)((*R*,*R*)-DPPN)]. ^{31}P NMR (400 MHz, $CDCl_3$) δ44.5 (s).
Trans-Ru[Cl_2((*S*)-Xyl-P-Phos)((*R*,*R*)-DPPN)]. ^{31}P NMR (400 MHz, $CDCl_3$) δ44.5 (s).

b) Preparation of Ru[Cl_2((*R*)-Xyl-BINAP)((*R,R*)-DPPN)].

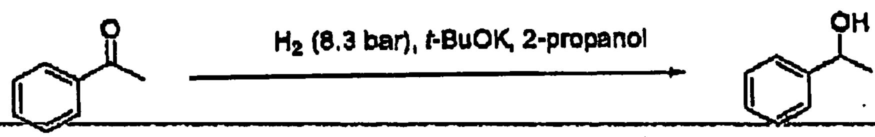
The above experiment was repeated combining (R)-Xyl-BINAP with [$RuCl_2$(benzene)] dimer and reacting this with the (R,R)-Dppn. The crude product was obtained by removal of the solvent. Trans-Ru[Cl_2((*R*)-Xyl-BINAP)((*R,R*)-DPPN)]. ^{31}P NMR (400 MHz, $CDCl_3$) δ 45.3 (s).

<u>Example 3: Hydrogenation Reactions using Dppn-catalysts</u>

General method: Asymmetric hydrogenation of ketones (substrate to catalyst ratio 1000/1): 2-propanol (2 mL), ketone (2 mmol) and 0.1 M potassium tert-butoxide (KO^tBu) (50 μL, 5×10^{-3} mmol) were added in turn to a 25 mL autoclave charged with the ruthenium catalyst (2×10^{-3} mmol), under inert atmosphere. The vessel was first purged with hydrogen three times and then pressurised with hydrogen to 8.3 bar. The reaction mixture was stirred at room temperature for the indicated time. The enantiomeric excess was determined by gas-chromatography using a Chirasil-DEX CB column.

Asymmetric hydrogenation of ketones (substrate to catalyst ratio = 2500/1): 2-propanol (4.4 mL), ketone (5 mmol) and 0.1 M KO^tBu (50 μL, 5×10^{-3} mmol) were added in turn to a 25 mL autoclave charged with the ruthenium catalyst (2×10^{-3} mmol), under inert atmosphere. The vessel was first purged with hydrogen three times and then pressurized with hydrogen to 145 psi. The reaction mixture was stirred at room temperature for the indicated time. The enantiomeric excess was determined by gas-chromatography using a Chirasil-DEX CB column.

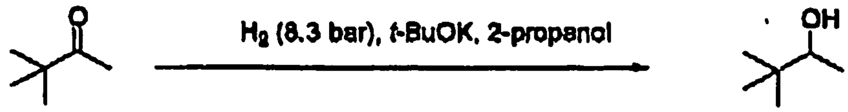
a) Hydrogenation of Acetophenone



Using the general method, the Dppn-catalysts of Example 2 gave the following results;

Catalyst	S/c	Time (hrs)	Conv. (%)	Ee (%)
(R)Xyl-P-Phos-$RuCl_2$-Dppn	1000	3	100	93
(R)Xyl-P-Phos-$RuCl_2$-Dppn	2500	3	100	95
(R)Xyl-P-Phos-$RuCl_2$-Dppn	2500	2.5	100	95
(R)Xyl-P-Phos-$RuCl_2$-Dppn	2500	6.5	96	95
(S)Xyl-P-Phos-$RuCl_2$-Dppn	1000	5	100	69
(S)Xyl-P-Phos-$RuCl_2$-Dppn	2500	6	100	74

b) Hydrogenation of pinacolone



Using the general method with the Dppn-catalysts of Example 2 gave the following results:

Catalyst	S/c	Time (hrs)	Conv.	Ee (%)
(R)Xyl-P-Phos-RuCl$_2$-Dppn	1000	16	48	65
(R)Xyl-BINAP-RuCl$_2$-Dppn	1000	16	48	60

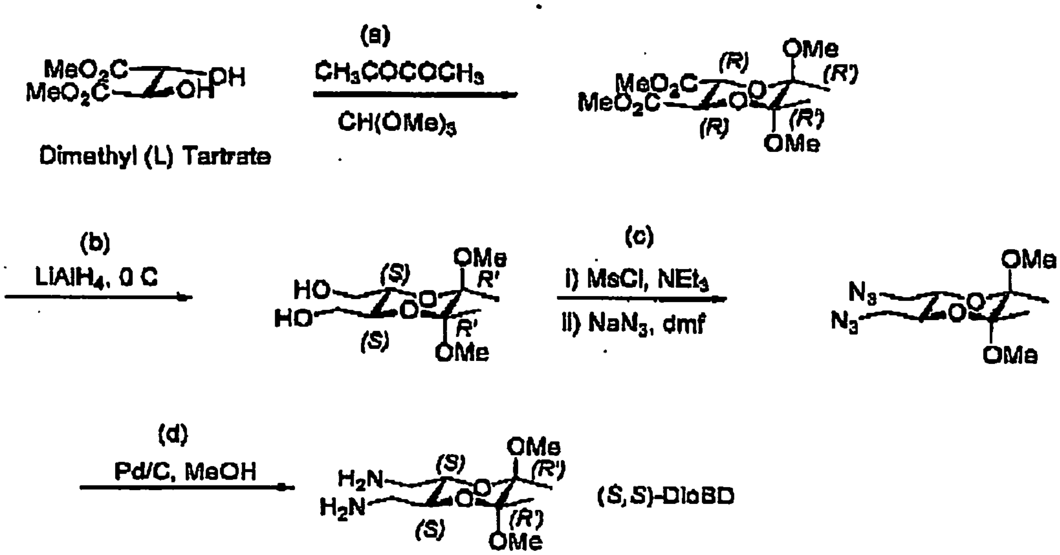
A comparative experiment was performed using the general method with a comparative 1,2-diamine catalyst based on 1,2-diphenylethylenediamine (Dpen).

Comparative Catalyst	S/c	Time (hrs)	Conv.	Ee (%)
(R)Xyl-BINAP-RuCl$_2$-(R,R)Dpen	1000	16	30	11

The results demonstrate that the Dppn-catalysts of Example 2 can give an improved yield and enantiomeric excess over the comparative 1,2-diamine catalyst.

<u>Example 4: Synthesis of (3-Aminomethyl-5-6-dimethoxy-5-6-Dimethyl[1,4]-dioxan-2-yl)-methylamine [(S,S)-DioBD]</u>

The intermediate diol was prepared according to literature procedure for steps (a) and (b). (Ley, J. Chem. Soc., Perkin Trans 1, 1999, 1627).



(S,S)-DioBD

(a) (3-hydroxymethyl-5-6-dimethoxy-5-6-Dimethyl[1,4]dioxan-2-yl]methylalcohol.
A mixture of dimethyl-(L)-tartrate (4.578 g, 0.0257 mol), 2,3-butadione (2.65 g, 0.0308 mol), trimethyl orthoformate (11.41 g, 0.0771 mol) and camphor sulphonic acid (0.597 g, 2.57 mmol) in anhydrous methanol was refluxed overnight (17 hrs) under nitrogen. The reaction was cooled and the solvent removed by rotary evaporation to give the crude product as a brown solid. The material was passed through a column of silica to give the pure product.

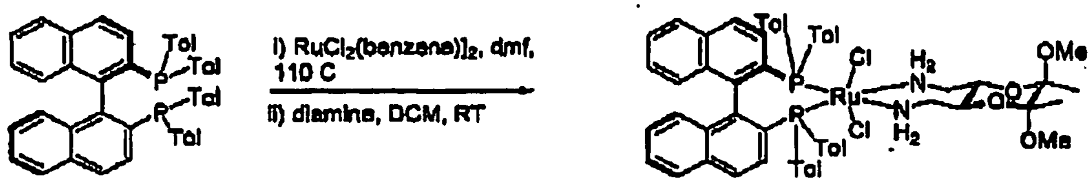
(b) To a solution of the diester (3.2 g, 0.011 mol) in dry THF at 0°C was added a solution of $LiAlH_4$ (1M, 11 ml, 0.011 mol) dropwise. After the addition was complete the reaction mixture was allowed to warm to room temperature and stirred for 1 hr. The reaction was then cooled to 0°C and ethylacetate (EtOAc) (5 ml) was added. The reaction mixture was then poured into saturated aqueous ammonium chloride solution and extracted with EtOAc (3x100ml). The solvent was removed to give the crude diol as a light brown solid, which was used without any further purification.

(c) (3-azidomethyl-5-6-dimethoxy-5-6-dimethyl[1,4]dioxan-2-yl]methylazide
To a solution of the diol (1.818 g, 7.69 mmol) and triethylamine (4.28 ml, 0.03 mmol) in dry THF (15 ml) at 0°C under N_2 was added dropwise methansulphonyl chloride (1.25 ml, 0.016 mol). The reaction mixture was allowed to warm to room temperature and the stirred for 1 h. The mixture was then filtered and the solid washed with THF (2x 5ml). The THF was removed in vacuo to give the crude product. To this crude product was added sodium azide (1.08 g, 0.0169 mol) and DMF (5 ml). The mixture was heated at 60°C for 14 hrs. Then the DMF was removed under high vacuum. MTBE was then added and the organic phase washed with water (3x100 ml) and brine, dried over anhydrous $MgSO_4$ and the solvent removed to give the crude product. The diazide was obtained by column chromatography eluting with hexane – EtOAc (9:1) to give the product as a white solid (0.8 g,).
^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.8 (1H, t, *J* 2.5, C*H*), 3.3 (1H, m, C*H*H), 3.25 (3H, s, OC*H*$_3$), 3.15 (1H, dd, J 13 and 2.5, CH*H*), 1.25 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) 100 (C), 69 (CH), 50.8 (CH_3), 48.1 (CH_2), 17.3 (CH_3).

(d) (3-Aminomethyl-5-6-dimethoxy-5-6-Dimethyl[1,4]dioxan-2-yl]methylamine [(S,S)DioBD]
A mixture of the diazide (0.8g, 2.79 mmol) and Pd/C (10 wt % Pd, 0.025 g) was stirred in an autoclave under H_2 (80psi) for 2 hrs. The H_2 was released and the mixture filtered through celite. The solvent was removed to give the diamine as initial a colourless oil which eventually solidified upon standing.
^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.52 (1H, m, CH), 3.2 (3H, s, OCH_3), 2.7 (2H, br d, J 4, CH_2), 1.25 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 98.5 (C), 71.1 (CH), 47.9 (CH_3), 42.6 (CH_2), 17.6 (CH_3).

Example 5: Preparation of DioBD catalysts

(a) Preparation of $Ru[Cl_2\{(R/S)\text{-Tol-BINAP}\}\{(S,S)\text{-DioBD}\}]$

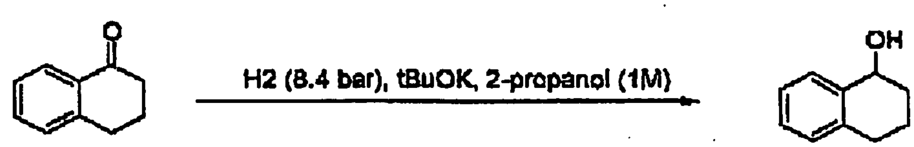


A solution of (R)- or (S)-TolBinap (100 mg, 0.147 mmol) and [$RuCl_2$(benzene)] dimer (37 mg, 0.0737 mmol) in Dimethylformamide (1 ml) was heated at 110°C for 15 mins under N_2. The dark red reaction mixture was cooled and the dmf removed in vacuo. To this crude complex was added a solution of the (*S*,*S*)-DioBD diamine (34 mg, 0.147 mmol) in dichloromethane (5 ml) under nitrogen. The yellowish solution was stirred at room temperature for 1 hr after which the solvent was removed in vacuo. The complex was extracted from the crude solid by addition of hexane:MTBE (1:1, 10 ml), filtration and removal of the solvent which resulted in the precipitation of a yellow solid. The solvent was completely removed and to give the complex as a yellow solid.

$Ru[Cl_2\{(S)\text{-Tol-BINAP}\}\{(S,S)\text{-DioBD}\}]$: ^{31}P NMR ($CDCl_3$, 400 MHz) δ 44.8
$Ru[Cl_2\{(R)\text{-Tol-BINAP}\}\{(S,S)\text{-DioBD}\}]$: ^{31}P NMR ($CDCl_3$, 400 MHz) δ 45.4

Example 6: Hydrogenation Reactions using DioBD-catalysts

(a) Hydrogenation of Tetralone



2-propanol (1 mL), tetralone (1 mmol) and 0.1 M KO^{t}Bu (50 µL, 5 x 10^{-3} mmol) were added in turn to a 25 mL autoclave charged with the ruthenium catalyst (2 x 10^{-3} mmol), under inert atmosphere. The vessel was first purged with hydrogen three times and then pressurized with hydrogen to 8.3 bar. The reaction mixture was stirred at room temperature for the indicated time. The enantiomeric excess was determined by GC using a Chirasil-DEX CB column. Using this method, the DioBD-catalyst of Example 5 gave the following results;

Catalyst	S/c	Time (hrs)	Conv.(%)	Ee (%)
(*S*)TolBINAP-$RuCl_2$-(*S*,*S*)-DioBD	500	16	23.5	81

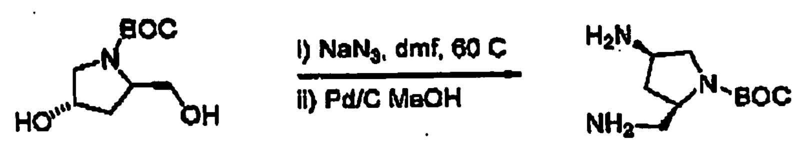
A comparative experiment was performed using the same method with a comparative 1,2-diamine catalyst based on 1,2-diphenylethylenediamine (Dpen).

Comparative Catalyst	S/c	Time (hrs)	Conv.	Ee (%)
(*S*)TolBINAP-RuCl$_2$-(*S,S*)-Dpen	500	16	98	24

The result demonstrates that the DioBD-catalysts of Example 5 can give an improved enantiomeric excess over the comparative 1,2-diamine catalyst.

Example 7: Synthesis of (2*S*,4*S*)-4-Amino-2-aminomethylpyrrolidine-1-carboxylic acid *tert*-butyl ester (PyrBD).

The synthesis is based on the commercially available trans diol. Ganesh (Organic Letters, 2001,3, 103), has reported the synthesis of these diamines for use as analogues that stabilise DNA duplexes and triplexes.



BOC = $CO_2C(CH_3)_3$

(2*S*,4*R*)-4-Methanesulfonyloxy-2-methanesulfonyloxymethylpyrrolidine-1-carboxylic acid *tert*-butyl ester: To a solution of alcohol (~15 mmol) and triethylamine (6.5 mL, 45 mmol) in THF (100 mL) was slowly added mesylchloride (MsCl) (2.6 mL, 33 mmol). After stirring for 30 min at room temperature, the precipitated salts were filtered off and the reaction mixture was treated with saturated aqueous NH_4Cl (100 mL). The aqueous phase was extracted with MTBE (2 x 75 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford 4.67 g (12.5 mmol, 83%) of a white solid which was used without further purification.

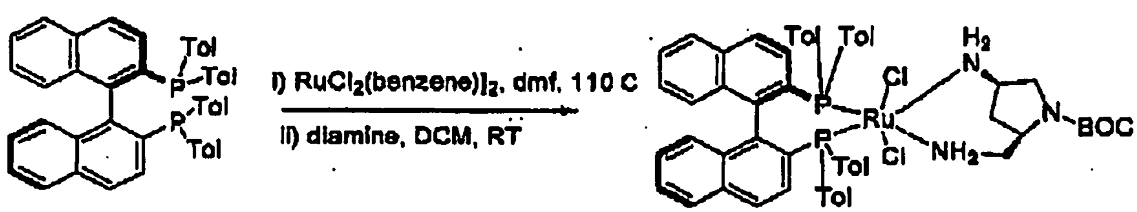
i) (2*S*,4*S*)-4-Azido-2-azidomethylpyrrolidine-1-carboxylic acid *tert*-butyl ester: A solution of mesylate (4.67 g, 12.5 mmol) and NaN_3 (2.43 g, 37.5 mmol) in DMF (50 mL) was heated at 90°C for 24 hrs. After cooling down to room temperature, the reaction mixture was diluted with MTBE (50 mL) and washed with H_2O (5 x 50 mL). The organic phase was then dried (anhydrous $MgSO_4$) and concentrated under reduced pressure to afford a solid which was used without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.1 (1H, br s), 3.9 (1H, br m), 3.65 (1H, br s), 3.5 – 3.2 (3H, br m), 2.2 (1H, m), 2.0 (1H, m), 1.4 (9H, s).

(ii) (2*S*,4*S*)-4-Amino-2-aminomethylpyrrolidine-1-carboxylic acid *tert*-butyl ester. A mixture of the diazide (0.8g, 2.79 mmol) and Pd/C (10 wt % Pd, 0.025 g) was stirred in an autoclave under hydrogen (80psi) for 2 hrs. The hydrogen pressure was released and the mixture filtered through celite. The solvent was removed to give the diamine as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.75 (2H, br s), 3.4 (1H, m), 3.0 – 2.7 (3H, m), 2.25 (1H, m), 1.5 – 1.3 (10H, m).

Example 8: Preparation of PyrBD catalysts

a) Preparation of Ru[Cl_2((*R*/*S*)-Tol-BINAP)((*S*,*S*)-PyrBD)]

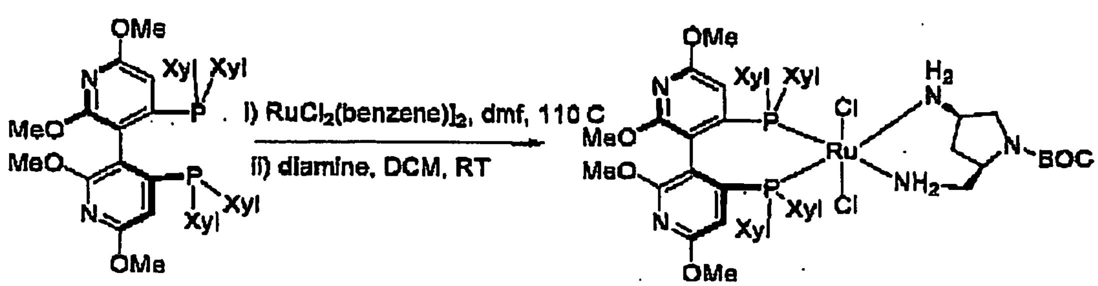


A solution of (R)- or (S)-Tol-Binap (100 mg, 0.147 mmol) and [$RuCl_2$(benzene)] dimer (37 mg, 0.0737 mmol) in Dimethylformamide (1 ml) was heated at 105°C for 15 mins under nitrogen. The dark red reaction mixture was cooled and the DMF removed in vacuo. To this crude complex was added a solution of the (*S*,*S*)-PyrBD diamine (34 mg, 0.147 mmol) in dichloromethane (5 ml) under nitrogen. The yellowish solution was stirred at room temperature for 1 hr after which the solvent was removed in vacuo. The complex was extracted from the crude solid by addition of hexane : MTBE (1:1, 10 ml), followed by filtration and removal of the solvent which resulted in the precipitation of a yellow solid. The solvent was removed under vacuo to give the complex as a yellow solid.

Ru[Cl_2((*R*)-Tol-BINAP)((*S*,*S*)-PyrBD)]: ^{31}P NMR ($CDCl_3$, 400 MHz) δ 45.2 (d, J 37) and δ 41.3 (d, J 37)

Ru[Cl_2((S)-Tol-BINAP)((*S*,*S*)-PyrBD)]: ^{31}P NMR ($CDCl_3$, 400 MHz) δ 44.5 (d, J 37) and δ 42.3 (d, J 37)

b) Preparation of Ru[Cl_2((*R*/*S*)-Xyl-P-Phos)((*S*,*S*)-PyrBD)]



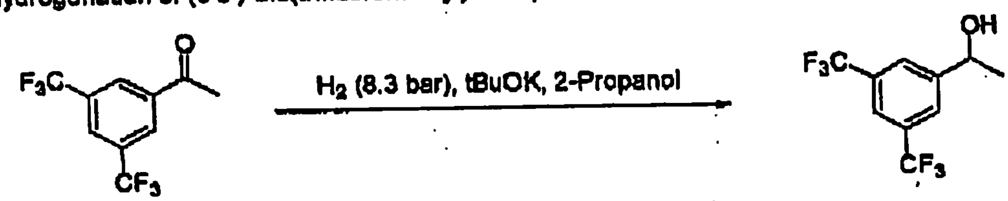
A solution of (R)- or (S)-Xyl-P-Phos (61 mg, 0.086 mmol) and [RuCl$_2$(benzene)] dimer (16.8 mg, 0.0315 mmol) in Dimethylformamide (1 ml) was heated at 100°C for 2.5 hrs under nitrogen. The dark red reaction mixture was cooled to room temperature. To this crude complex was added a solution of the (*S,S*)-PyrBD diamine (0.067 mmol) in dichloromethane (1 ml) under nitrogen. The brown solution was stirred at room temperature overnight after which the solvent was removed in vacuo to yield the crude complex as a brown solid.

Ru[Cl$_2${(*R*)-Xyl-P-Phos}{(*S,S*)-PyrBD}]: ^{31}P NMR (CDCl$_3$, 400 MHz) δ 45.2 (d, J 37) and δ 41.3 (d, J 30)

Ru[Cl$_2${(S)-Xyl-P-Phos}{(*S,S*)-PyrBD}]: ^{31}P NMR (CDCl$_3$, 400 MHz) δ 44.6 (d, J 37) and δ 41.7 (d, J 37)

Example 9: Hydrogenation Reactions using PyrBD-catalysts

a) Hydrogenation of (3'5')-bis(trifluoromethyl)acetophenone



Hydrogenation was performed according to the general method described in Example 3. The PyrBD-catalysts of Example 8 gave the following results;

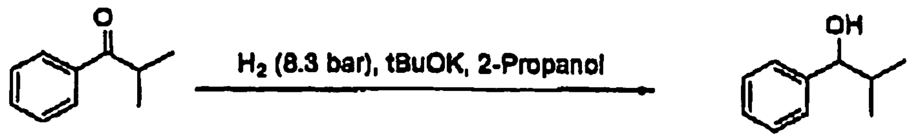
Catalyst	S/c	Time (hrs)	Conv. (%)	Ee (%)
(S)Xyl-P-Phos-RuCl$_2$-PyrBD	1000	16	>98	69
(R)Xyl-P-Phos-RuCl$_2$-PyrBD	1000	16	>98	91

A comparative experiment was performed using the general method with a comparative 1,2-diamine catalyst based on 1,2-diphenylethylenediamine (Dpen).

Comparative Catalyst	S/c	Time (hrs)	Conv.	Ee (%)
(R)Xyl-P-Phos-RuCl2-(R,R)Dpen	1000	16	>98	60

The result demonstrates that the PyrBD-catalysts of Example 8 can give an improved enantiomeric excess over the comparative 1,2-diamine catalyst.

b) Hydrogenation of Isobutyrophenone



Hydrogenation was performed according to the general method described in Example 3. The PyrBD-catalyst of Example 8 gave the following results;

Catalyst	S/c	Time (hrs)	Conv.(%)	Ee (%)
(*S*)TolBINAP-RuCl$_2$-(*S,S*)PyrBD	1000	14	>98	80

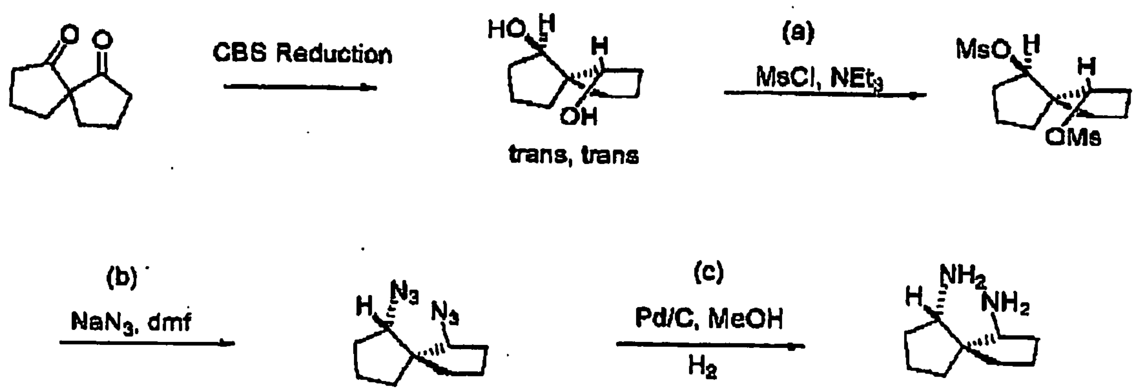
A comparative experiment was performed using the general method with a comparative 1,2-diamine catalyst based on 1,2-diphenylethylenediamine (Dpen).

Comparative Catalyst	S/c	Time (hrs)	Conv.	Ee (%)
(S)TolBINAP-RuCl$_2$-(*S,S*)Dpen	1000	48	81	87

The result demonstrates that the PyrBD-catalysts of Example 8 can give an improved acivity and yield with comparable enantiomeric excess with the comparative 1,2-diamine catalyst.

Example 10:Preparation of *cis,cis*-SpiroDiamine

The *trans,trans* SpiroDiol Intermediate was prepared according to literature procedure report by Chan (*Tetrahedron Letters*, **2000**, 4425).



(a) *Cis,Cis* Spiro-mesylate: To a solution of *trans,trans* diol (0.27 g, 1.74 mmol) and triethylamine (0.97 ml, 6.97 mmol) in THF (5 mL) was slowly added mesyl chloride (MsCl) (0.29 ml, 3.83 mmol). After stirring for 60 minutes at room temperature, the precipitated salts

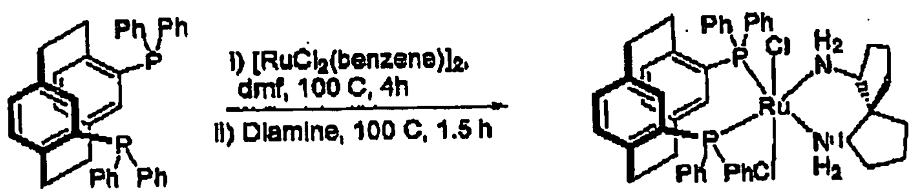
were filtered off and washed with a further portion of THF (8 ml). The solvent was removed in vacuo to yield the crude product of a white solid that was used into the next reaction without further purification.

(b) *Cis, cis* - Spirodiazide: A solution of mesylate (from previous step) and sodium azide, NaN_3 (0.339 g, 5.2 mmol) in DMF (2.5 mL) was heated at 90°C for 17 hrs. After cooling down to room temperature, the reaction was diluted with MTBE (50 mL) and washed with H_2O (5 x 50 mL). The organic phase was then dried (anhydrous $MgSO_4$) and concentrated under reduced pressure to afford the crude product. Flash column chromatography eluting with hexane followed by hexane – ethyl acetate (4:1) gave the cis, cis diazide. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.7 (2H, s, CH), 2.0 – 1.0 (6H, m, CH_2).

(c) *Cis, cis* – SpiroDiamine: A mixture of the diazide (0.1 g) and Pd/C (10 wt % Pd, 0.010 g) was stirred in an autoclave under hydrogen (80psi) for 2 hrs. The H_2 pressure was released and the mixture filtered through celite. The solvent was removed to give the diamine as a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.1 (2H, d, CH), 2.0 – 1.0 (6H, m, CH_2).

Example 11: Preparation of *cis,cis*-SpiroDiamine catalysts

a) Preparation of Ru[Cl_2((*R*)-PhanePHOS}{(*cis,cis*)-SpiroDiamine }]

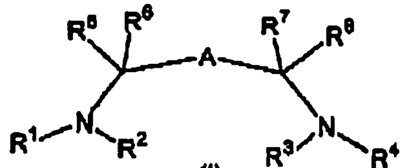


(R)-PhanePHOS (33 mg, 0.058 mmol) and [Ru(benzene)Cl]$_2$ (14.7 mg, 0.0294 mmol) were placed in a Schlenk flask and the air was replaced with nitrogen. Anhydrous, degassed DMF (1.5 ml) and toluene (2 ml) were added. The mixture was then heated at 105°C for 4 hours. A red homogeneous solution was obtained. To the solution was then added solid cis,cis-SpiroDiamine (0.05889 mmol) and the solution heated again for 1.5 hrs at 105°C. The solvent was then removed under vacuo. The resulting solid was dissolved in CH_2Cl_2 and MTBE added. Removal of the solvent caused precipitation of a tan coloured solid. The solid was not collected but the solvent completely removed to give the crude complex, which was used without any further purification.

Ru[Cl_2((*R*)-Phanephos}{(*cis,cis*)-SpiroDiamine }]: ^{31}P NMR ($CDCl_3$): 44.68 ppm.

Claims.

1. A chiral catalyst comprising the reaction product of a group 8 transition metal compound a chiral phosphine and a chiral diamine of formula (I)



(I)

in which R^1, R^2, R^3 or R^4 are independently hydrogen, a saturated or unsaturated alkyl, or cycloalkyl group, an aryl group, a urethane or sulphonyl group and R^5, R^6, R^7 or R^8 are independently hydrogen, a saturated or unsaturated alkyl or cycloalkyl group, or an aryl group, at least one of R^1, R^2, R^3 or R^4 is hydrogen and A is a linking group comprising one or two substituted or unsubstituted carbon atoms.

2. A catalyst according to claim 1 wherein the group 8 metal compound is a compound of ruthenium.

3. A catalyst according to claim 1 or claim 2 wherein the chiral phosphine is a chiral bis(phosphine).

4. A catalyst according to any one of claims 1 to 3 wherein R^1, R^2, R^3 and R^4 are the same or different and are selected from hydrogen, methyl, ethyl, isopropyl, cyclohexyl, phenyl or 4-methylphenyl groups.

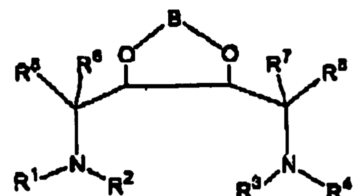
5. A catalyst according to any one of claims 1 to 3 wherein R^1 and R^2 are linked or R^3 and R^4 are linked so as to form a 4 to 7-membered ring structure incorporating the nitrogen atom.

6. A catalyst according to any one of claims 1 to 5 wherein R^5, R^6, R^7 and R^8 are the same or different and are selected from hydrogen, methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, sec-butyl, tert-butyl, cyclohexyl or substituted or unsubstituted phenyl or naphthyl groups.

7. A catalyst according to any one of claims 1 to 5 wherein one or more of R^5, R^6 R^7 or R^8 form one or more ring structures with the linking group A.

8. A catalyst according to any one of claims 1 to 7 wherein a substituting group on the carbon atom of linking group A is alkyl (C1-C20), alkoxy (C1-C20) or amino or forms one or more ring structures incorporating one or more carbon atoms making up the linking group.

9. A catalyst according to any one of claims 1 to 3 wherein the chiral diamine is of formula (II)

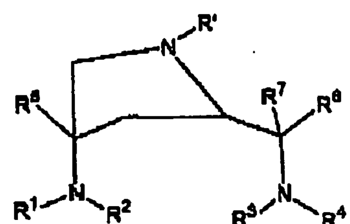


(II)

wherein B is a linking group comprising one or two substituted or unsubstituted carbon atoms.

10. A catalyst according to claim 9 wherein R^1, R^2, R^3, R^4 are hydrogen, R^5, R^6, R^7 and R^8 are hydrogen or alkyl groups and B comprises $C(CH_3)_2$ or $(CH_3)(OCH_3)C\text{-}C(CH_3(OCH_3)$.

11. A catalyst according to any one of claims 1 to 3 wherein the chiral diamine is of formula (III)

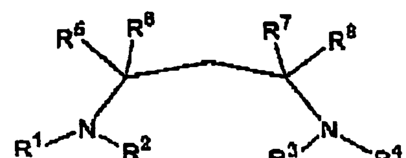


(III)

wherein R' is a protecting group.

12. A catalyst according to claim 11 wherein R^1, R^2 and R^5 are hydrogen, R^3 and R^4 are hydrogen or alkyl, R^7 and R^8 are hydrogen, alkyl or aryl and R' is selected from an alkyl, aryl, carboxylate, amido or sulphonate protecting group.

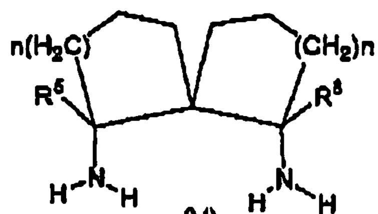
13. A catalyst according to any one of claims 1 to 3 wherein the chiral diamine is of formula (IV)



(IV)

14. A catalyst according to claim 13 wherein R^1, R^2, R^3, R^4, R^6, R^7 are hydrogen and R^5 and R^8 are aryl or substituted aryl groups

15. A catalyst according to any one of claims 1 to 3 wherein the chiral diamine is of formula (V).



(V)

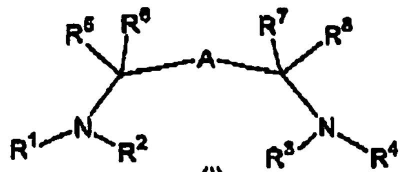
wherein n = 1 or 2.

16. A catalyst according to claim 15 wherein R^5 and R^8 are hydrogen.

17. The use of catalysts of claims 1 to 16 for the asymmetric hydrogenation of ketones and imines.

Abstract

Catalysts suitable for asymmetric hydrogenation reactions is described comprising the reaction product of a group 8 transition metal compound a chiral phosphine and a chiral diamine of formula (I)



(I)

in which R^1, R^2, R^3 or R^4 are independently hydrogen, a saturated or unsaturated alkyl, or cycloalkyl group, an aryl group, a urethane or sulphonyl group and R^5, R^6, R^7 or R^8 are independently hydrogen, a saturated or unsaturated alkyl or cycloalkyl group, or an aryl group, at least one of R^1, R^2, R^3 or R^4 is hydrogen and A is a linking group comprising one or two substituted or unsubstituted carbon atoms.

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